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ORIGINAL ARTICLE

Neonatal Sepsis: A 6-Year Analysis in a Neonatal Care Unit in Taiwan

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Background: Neonatal sepsis is the most serious problem in neonatal intensive care, resulting in significant morbidity and mortality. We evaluated the causative pathogen, drug sensitivity, hematological parameters, clinical course and mortality rate of neonatal sepsis in a Taiwanese medical center and compared our results to those of previous studies conducted in Taiwan.
Methods: Neonates admitted to the neonatal intensive care unit (NICU) at National Taiwan University Hospital (NTUH) between January 2001 and December 2006 were included in this study. Patients were divided into early-onset sepsis and late-onset sepsis groups if their culture tested positive within the first 7 days of life or later, respectively.
Results: A total of 109 episodes of sepsis were identified in 100 neonates. The incidence of sepsis was 4.06% among all NICU admissions. Most neonates with early-onset sepsis were term infants, while very low birth weight (VLBW) and preterm infants accounted for the majority of cases of late-onset sepsis. In early-onset sepsis, the most common pathogens responsible included group B streptococci (GBS) (36%) and *Escherichia coli* (*E. coli*) (26%). GBS was associated with more meningitis involvement but lower incidence of mortality compared with *E. coli*. The most common causative microorganisms in late-onset sepsis were coagulase-negative staphylococci (CONS) (40%) and Candida (15%). The sepsis-related mortality rates were higher in early-onset sepsis (10%) than in late-onset sepsis (7%).
Conclusion: Unlike previous reports from Taiwan, in the present study, GBS was found to be the leading pathogen in early-onset sepsis. GBS screening and intrapartum antibiotic prophylaxis guidelines should be used in Taiwan to prevent early neonatal sepsis. The most common causative microorganisms of late-onset sepsis were CONS and Candida species. *Candida parapsilosis* was associated with a high mortality rate.

1. Introduction

Neonatal sepsis remains the most serious problem in neonatal intensive care and results in significant morbidity and mortality, particularly in very low birth weight (VLBW) preterm infants. Because temporal and geographic differences in pathogens associated with neonatal sepsis have been observed,

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it is important to recognize the common pathogens and associated drug sensitivities for individual hospitals. Empiric antibiotic therapy will be ineffective if the decision is not made according to the ordinary causative microorganism in each specific, neonatal intensive care unit (NICU).

Here, we evaluated the causative pathogen, incidence, clinical course and mortality rate of neonatal sepsis over a 6-year period in a Taiwanese medical center. We compared our findings with those of previous studies conducted in Taiwan.

2. Materials and Methods

Infants admitted to the NICU at the National Taiwan University Hospital (NTUH) between January 2001 and December 2006 were included in this study. Patients' chart records were retrospectively reviewed for gestational age, birthweight, pathogen, symptoms and signs, age at onset of sepsis, time between central line insertion and removal days, duration of ventilator use, hematocrit, C-reactive protein (CRP) and mortality. NTUH is a teaching hospital that provides tertiary care in the northern part of Taiwan. It has a level three NICU with a total of 24 beds. Each NICU nurse cares for two or three babies. There are four attending neonatologists, four neonatal fellows, four pediatric residents and two intern doctors working in the NICU.

Approximately 0.5–1 mL of blood was drawn in sterile conditions after peripheral puncture. The antimicrobial hand washing solutions used are Hibiscrub and Better-Iodine. Visitors are restricted to two per bed at one time and are required to wash their hands and wear cover gowns. Prophylactic antifungal treatment is not used in this NICU. Proportions were compared by χ^2 test. Relative risks were estimated to examine the association between birth weight and rate of late-onset sepsis.

2.1. Definitions

Sepsis was defined by a positive blood and/or cerebrospinal fluid (CSF) culture and unstable vital signs. Patients were divided into those with sepsis that developed within the first 7 days of life (early-onset sepsis) and those with sepsis that developed after 7 days of life (late-onset sepsis).[1] A few infants had more than one episode of sepsis. If the organism was cultured after 10 days of appropriate antibiotic therapy or a different organism was cultured from a subsequent culture, this was considered an additional episode.[2] Deaths were attributed to sepsis if they occurred within 7 days of a positive culture.[3,4] Catheter-related sepsis was defined as both a positive blood culture and a positive intravascular catheter tip culture involving the same microorganism without another infection source.[1] Nosocomial infection was defined as sepsis occurring 48 hours after admission.

Cases with positive cultures for coagulase-negative staphylococci (CONS) were classified as definite infection, possible infection or contamination.[2,5] Definite infection was defined by two positive cultures of blood specimens drawn within 2 days or one positive culture with a blood CRP level greater than 1 mg/dL within 2 days after blood culture. Possible infection was defined by one positive culture and treatment for at least 5 days with an anti-staphylococcal agent or another drug to which the organism was susceptible. Contamination was defined as one positive culture without elevated CRP or antibiotic therapy. Cases with definite or possible CONS sepsis were included in our analysis.

3. Results

3.1. Incidence

Between January 1, 2001 and December 31, 2006, 2727 neonates were admitted to the NICU. Of these, 100 neonates with 109 episodes of sepsis were included in this study. The incidence of sepsis was 4.00% among all NICU infants, or 2.70 per 1000 patient-days. There were 28 episodes in 28 infants of early-onset sepsis and 81 episodes in 72 infants of late-onset sepsis. Of these, two (7%) episodes of early-onset sepsis and 64 (79%) episodes of late-onset sepsis occurred in VLBW infants ($p<0.05$). The gender, gestational age, birth weight and mode of delivery of these patients are shown in Table 1. The late-onset sepsis rates and patient-day rates stratified by birth weight group are shown in Table 2.

Ninety-three (93%) infants had a single episode of sepsis. Five (5%) infants had two episodes and two infants had three episodes of sepsis; all but one of these infants were of VLBW. The causative pathogens are shown in Table 3. The mean age of onset of lateonset sepsis was 25.3 days of age (range: 7–95 days).

3.2. Distribution of pathogens

In infants with early-onset sepsis, group B streptococci (GBS) (36%) was the major causative pathogen, followed by *Escherichia coli* (*E. coli*) (26%) and CONS (13%). On the other hand, the most common microorganism in late-onset sepsis was CONS (40%), followed by Candida (15.4%) and *Staphylococcus aureus* (SA) (13%). Overall, gram-positive microorganisms accounted for 65% of cases of neonatal sepsis, followed by gram-negative microorganisms and

Table 1 Gender, gestational age, birth weight and mode of delivery of infants with early-onset and late-onset neonatal sepsis

	Early-onset *n* (%)	Late-onset *n* (%)	Total *n* (%)	*p*-value
Episodes of sepsis	28	81	109	
Number of infants	28	72	100	
Inborn:Outborn	7:21	9:63	16:84	
Gender				
Males:Females	2.1:1	1.3:1	1.5:1	
Male	19 (67.9)	46 (56.8)	65	
Female	9 (32.1)	35 (43.2)	44	
Gestational age				
Median (range)	38 (23–40)	28 (22–40)	29 (22–40)	<0.05
<28 wk	1 (3.5)	38 (46.9)	39 (35.8)	
28–32 wk	1 (3.5)	30 (37.0)	31 (28.4)	
33–36 wk	4 (14.3)	1 (1.2)	5 (4.6)	
>36 wk	22 (78.6)	12 (14.8)	34 (31.2)	
Birth weight				
Median (range)	2780 (636–4130)	1050 (522–3500)	1172 (522–4130)	<0.05
≤1000 g	1 (3.5)	37 (45.7)	38 (34.8)	
1001–1500 g	1 (3.5)	27 (33.3)	28 (25.6)	
1501–2000 g	3 (10.7)	6 (7.4)	9 (8.3)	
2001–2500 g	4 (14.3)	1 (1.2)	5 (4.6)	
>2500 g	19 (67.9)	10 (12.3)	29 (26.6)	
Mode of delivery				
Vaginal delivery:Cesarean section	1.7:1	0.5:1	0.8:1	<0.05
Vaginal delivery	18 (64.3)	30 (37.0)	48 (44.0)	
Cesarean section	10 (35.7)	51 (63.0)	61 (56.0)	

Table 2 Rate of birth weight-specific late-onset neonatal sepsis

Birth weight (g)	Sepsis episodes (*n*)	Admissions (*n*)	Admission patient-days	Sepsis patient rate (%)	Sepsis patient-day rate (per 1000 patient-days)	RR
≤1000	37	273	12,128	13.6	3.0	3.33
1001–1500	27	317	10,523	8.5	2.6	2.89
1501–2000	6	399	5994	1.5	1.0	1.11
>2000	11	1738	11,732	0.6	0.9	1

RR = relative risk.

Candida (25% and 11%, respectively). Five episodes of sepsis were due to polymicrobial infection.

3.3. Mortality and morbidity

In total, 20 (20%) of the 100 infants died. Nine infants (8%) died within 7 days of septic episodes. Six (21%) of these infants were in the early-onset sepsis group and 14 (19%) were in the late-onset sepsis group. Three (10%) infants with early onset sepsis and six (7%) infants with late-onset sepsis died within 7 days after the onset of sepsis, and their deaths were considered sepsis-related. In those with early-onset sepsis, the sepsis-related mortality rates were 25% for *E. coli* infection, but zero for GBS and Methicillin-resistance coagulase-negative staphylococci (MRCONS) infection. The mortality rates for the major pathogens in patients with late-onset sepsis were 22% (2/9), 3% (1/34) and 11% (1/9) for *Candida parapsilosis*, MRCONS and Methicillin-resistance *Staphylococci aureus* (MRSA), respectively. Overall, the highest sepsis-related fatality rate was

Table 3 Pathogens isolated from patients with early-onset and late-onset neonatal sepsis

Pathogens	Early-onset		Late-onset		Total	
	Episodes *n* (%)	Attributable mortality*	Episodes *n* (%)	Attributable mortality*	Episodes *n* (%)	Attributable mortality*
Gram-positive						
MRCONS	4 (13%)	0	34 (40%)	1 (3%)	38	1 (2.6%)
GBS	11 (36%)	0	1 (1%)	0	12	0
MRSA			9 (11%)	1 (11%)	9	1 (11%)
MSSA			2 (2%)	0	2	0
Enterococcus faecalis	1 (3%)	0	5 (6%)	0	6	0
Enterococcus faecium			2 (2%)	0	2	0
Streptococcus bovis II			1 (1%)	0	1	0
Streptococcus pneumoniae			1 (1%)	1 (100%)	1	1 (100%)
Listeria monocytogenes	1 (3%)	0			1	0
Clostridium tertium	1 (3%)	1 (100%)			1	1 (100%)
Gram-negative						
E. coli	8 (26%)	2 (25%)	1 (1%)	0	9	2 (22%)
Klebsiella pneumoniae	1 (3%)	1 (100%)	6 (7%)	0	7	1 (14%)
Enterobacter cloacae	1 (3%)	0	3 (4%)	0	4	0
Pseudomonas aeruginosa	1 (3%)	0	3 (4%)	0	4	0
Stenotrophomonas maltophilia			1 (1%)	1 (100%)	1	1 (100%)
Acinetobacter baumannii			1 (1%)	0	1	0
Enterobacter aerogenes			1 (1%)	0	1	0
Bacillus species	1 (3%)	0			1	0
Fungi						
Candida parapsilosis			9 (11%)	2 (22%)	9	2 (22%)
Candida albicans			3 (3%)	0	3	0
Candida species			1 (1%)	0	1	0
Total	30	3/28 (10.7%)†	84	6/81 (7.4%)‡	104	9/109 (8.2%)

*Attributable mortality: neonate died within 7 days of sepsis onset; †3 infants died within 28 sepsis episodes, 2 polymicrobial infections; ‡6 infants died within 81 sepsis episodes, 3 polymicrobial infections; GBS=group B streptococci; MRCONS=methicillin-resistance coagulase-negative staphylococci; MRSA = methicillin-resistance *Staphylococci aureus*; MSSA=methicillin-sensitive *Staphylococci aureus*.

15% for Candida infection, followed by 8% and 7% for gram-positive and gram-negative microorganisms, respectively.

CSF studies were performed in 96% (27/28) of episodes of early-onset sepsis and 47% (38/81) of episodes of late-onset sepsis. The meningitis rates, defined by positive CSF culture, were 26% (7/27) and 5% (2/38) for early- and late-onset sepsis, respectively. Of the early-onset sepsis pathogens, GBS (36%) had a higher meningitis rate than *E. coli* (25%).

3.4. Sensitivity to antibiotics

There were nine episodes of *E. coli* sepsis, of which eight were early-onset and one was late-onset sepsis. Five of the nine isolates (55%) were resistant to ampicillin, and three (33%) were resistant to gentamicin. Extended-spectrum β-lactamases (ESBL) strain *E. coli* was present in one infant, who died at 3 days of age due to necrotizing enterocolitis with bowel perforation. Seventy-eight percent (7/9) of *S. aureus* isolates were methicillin-resistant. All CONS isolates were methicillin-resistant.

3.5. Hematological parameters

White blood cell (WBC) counts and differential counts drawn on the first day of sepsis were available for 108 and 92 episodes, respectively. The mean WBC was 10,784/mm^3 (range: 1160–87,310/mm^3). Leucopenia (WBC <5000/mm^3) and neutropenia (absolute neutrophil count: <2750/mm^3) were observed in 27% (29/108) and 34% (31/92) of episodes, respectively. An I/T (immature form of neutrophil/total neutrophil count) ratio greater than 0.2 was observed in 27% (25/92) of events. Only 5% (6/108) of episodes

were accompanied by leukocytosis (WBC >25,000/mm^3). CRP levels drawn on the first day of sepsis were elevated in 58% (56/97) of events. On the second day of sepsis, elevated CRP levels were recorded in 11 out of 12 infants.

3.6. Clinical symptoms and signs

Respiratory distress (60%), cyanosis (39%), fever (36%) and poor activity (36%) were the most common clinical presentations in early-onset sepsis. In contrast, desaturation (70%), bradycardia (48%), apnea (47%) and poor activity (43%) were most common in late-onset sepsis.

3.7. Therapeutic interventions

Of all episodes of late-onset sepsis, central line insertion was reported in 40 of 81 (49%) episodes during sepsis onset. The mean duration from central line insertion to onset of sepsis was 14 days. Catheter-related sepsis was observed in 20 cases. The leading causative pathogen was Candida (8/20), followed by CONS (5/20) and MRSA (2/20). Endotracheal tube placement with a mechanical ventilator was recorded in 16 infants with late-onset sepsis during infection (19%). The mean duration between endotracheal tube insertion to onset of sepsis was 19 days (range: 2–77 days).

4. Discussion

The incidence rate of sepsis in our study was 4.00% among all NICU admissions, and the nosocomial infection rate was 3.2%. A study by Jiang et al, also conducted in Taiwan, showed a 3.01% neonatal sepsis rate among all admissions and a 2.7% nosocomial sepsis rate.[3] Another prospective study in Taiwan revealed a 4.7% nosocomial sepsis rate.[6] The majority of infants (79%) suffering from late-onset sepsis were of VLBW. The relative risk for late-onset sepsis was higher in the lower birth weight groups. In contrast, VLBW infants accounted for only 7% of cases of early-onset sepsis. The premature and VLBW babies were at increased risk of nosocomial infection because of more aggressive and invasive therapies, such as indwelling central lines, mechanical ventilation, parenteral hyperalimentation and longer hospital stay.[2,7]

The pathogens responsible for neonatal sepsis in Taiwan appear to have changed over time (Tables 3 and 4). In our study, GBS was found to be the most common causative pathogen (36%) in early-onset sepsis in our study. In contrast, GBS was responsible for 6% of cases of early-onset sepsis in the reports by Wei et al (1981–1983), and increased to 18.1% the study by Jiang et al (1992–2001) and 28.6% the study by Lee et al (1999–2001).[3,8,9] In contrast, *S. aureus* accounted for 3.6–14% of cases of early-onset sepsis in previous studies but was not found in our study.[3,9,10] The proportion cases of early-onset sepsis caused by *E. coli* has remained steady, accounting for 26% of cases in our study, which is comparable with the other reports from Taiwan.[3,9] Fungal infection is a increasing problem in late-onset sepsis and nosocomial infection. We found that 15% of the pathogens causing late-onset sepsis were Candida, a proportion much higher than that previously recorded.[3,10,11]

GBS and *E. coli* were the most commonly observed pathogens in early-onset sepsis, as in other countries.[1,3,5,12,13] After implementation of intrapartum antibiotic prophylaxis (IAP) guidelines, the rate of early-onset GBS infection declined by 70% in the United States. *E. coli* has also replaced GBS as the leading cause of early-onset sepsis in VLBW.[5] In Taiwan, the GBS colonization rate in third-trimester pregnant women was 11.1–15%.[14,15] However, screening is not performed universally. This may explain the high proportion of GBS infection observed in our study. GBS screening and IAP guidelines should be popularized in Taiwan to prevent neonatal early-onset sepsis.

The increased incidence of *E. coli* sepsis in early-onset sepsis has recently become a problem in the United States.[5] Gram-negative sepsis is particularly lethal. The increasing resistance of *E. coli* isolates to ampicillin may be due to maternal intrapartum ampicillin prophylaxis.[5,16,17] Ampicillin- and gentamicin-resistant *E. coli* were isolated in 55% and 33%, respectively, of neonates in our study. Ampicillin and gentamicin are widely used as initial therapy for suspected early-onset sepsis in our practice. Cefotaxmin should replace gentamicin in such infants to treat possible resistant strains. The overall ampicillin-resistance of *E. coli* was 79% in our hospital in 2006.

CONS was the most common pathogen that caused neonatal late-onset sepsis in our study, as in previous reports.[2,3,6,7] The main problem was distinguishing true blood infections from contaminations. The sepsis-related mortality was 3% in our study, which is compatible with other reports.[2,18,19] The widespread use of vancomycin in NICUs may result in vancomycin-resistant strains of pathogens such as enterococci. A multicenter survey of neonatologists' practices in the treatment of neonates with suspected late-onset sepsis found that, in 83% of centers surveyed, at least 75% of survey respondents had similar practices with regard to prescribing a vancomycin-containing regimen for empiric therapy.[20] Karlowicz reported that substitution of oxacillin for vancomycin as the empiric antibiotic

Table 4 Neonatal sepsis analyses in Taiwan

	Ku-Nein Wei[9]		Jia-Horng Jiang[3]		Ya-Chun Tseng[11]	Sung-His Wei[10]	Ni-Chung Lee[8]	
Years	1981–1983		1992–2001		1997–1999	1997–2003	1999–2001	
Case numbers	160		270			208	58	
Episodes	165		325		137	232	85	
Population	Early and late onset		Early and late onset		Nosocomial	Nosocomial	Early and late onset	
Hospital	Mackay Memorial Hospital		Mackay Memorial Hospital		China Medical University Hospital	China Medical University Hospital	Taipei Veterans General Hospital	
	Early onset	Late onset	Early onset	Late onset	Nosocomial	Nosocomial	Early onset	Late onset
Gram-positive								
GBS	3 (6)	1 (0.9)	15 (18.1)	3 (1.1)			2 (28.6)	
SA	7 (14)	17 (14.8)	3 (3.6)	41 (15.2)	25 (18.5)	46 (18.0)	1 (14.3)	18 (22.5)
CONS	2 (4)	4 (3.5)	11 (13.2)	60 (22.2)	3 (2.2)	5 (2.0)	2 (28.6)	23 (28.8)
Enterococcus					6 (4.4)	12 (4.7)		2 (2.5)
Others	4 (8)	7 (6.0)	12 (14.5)	15 (5.6)		8 (3.1)		
Gram-negative								
E. coli	10 (20)	22 (19.1)	18 (21.7)	26 (9.6)	13 (9.6)	17 (6.6)		
Klebsiella pneumoniae	4 (8)	14 (12.2)	3 (3.6)	22 (8.2)	16 (11.9)	20 (7.8)	2 (28.6)	8 (10)
Enterobacter	3 (6)	5 (4.3)			11 (8.1)	12 (4.7)		18 (22.5)
Pseudomonas aeruginosa	11 (22)	15 (13.0)	5 (6.0)	15 (5.6)	11 (8.1)	21 (8.2)		
Stenotrophomonas maltophilia					6 (4.4)	7 (2.7)		
Acinetobacter baumannii	1 (2)	6 (5.2)		26 (9.6)	22 (16.3)	39 (15.2)		4 (5)
Others	5 (10)	24 (20.7)	16 (19.3)	45 (16.7)	11 (8.1)	40 (15.6)		1 (1.2)
Fungi	–	–						6 (7.5)
Candida albicans				9 (3.3)	8 (5.9)	19 (7.4)		
Candida guilliermondi				3 (1.1)				
Others				5 (1.9)		10 (3.9)		

CONS = coagulase-negative staphylococci; GBS = group B streptococci; SA = *Staphylococci aureus*.

for suspected gram-positive sepsis had no effect on the frequency of fulminate sepsis for CONS.[19] In our practice, the empiric antibiotics are ampicillin or oxacillin for suspected late-onset sepsis, and vancomycin is used in toxic infants. Twenty-one (61%) infants who had CONS late-onset sepsis did not receive vancomycin therapy as empiric antibiotics before their blood culture report. However, all CONS in our study were methicillin-resistant strains, and all infected infants ultimately received vancomycin therapy.

In late-onset sepsis, Candida species accounted for the second greatest number of cases. The most prevalent pathogens were *Candida albicans* and *C. parapsilosis*. *C. albicans* has been previously reported as the leading cause of neonatal sepsis.[2,21,22] However, *C. parapsilosis* was the most common species in our study. In recent reports, *C. parapsilosis* was the predominant fungal infection in some NICUs.[23] Evidence suggests that the growth and adherence of *C. parapsilosis* is enhanced in high glucose and certain hyperalimentation solutions.[24] The central venous catheter insertion site is reported to provide a portal of entry for fungi. An association between the insertion of a central venous catheter with *C. parapsilosis* sepsis has been reported.[25,26] Indwelling central venous catheters and hyperalimentation solution are both essential

treatments for VLBW infants; therefore, it is unsurprising that *C. parapsilosis* is becoming an increasingly common pathogen in these infants. Hospital personnel frequently carry Candida species on their hands, with *C. parapsilosis* being the most common species identified.[27,28] Restrictive hand-washing procedures in the NICU might lower horizontal transmission of *C. parapsilosis* and prevent Candida sepsis.

Early diagnosis of neonatal sepsis is important, but clinical signs are neither specific nor uniform. Many markers have been developed for early detection, including cell-surface markers (CD11b, CD64 and CD69), chemokines and cytokines (IL-6, IL-8, IL-10) and acute phase reactants (CRP, procalcitonin, serum amyloid A and inter-alpha inhibitor protein).[29,30] However, no single infection marker is sensitive and specific enough to convince a doctor to withdraw antibiotics therapy in a sick infant. Developing diagnostic tools such as DNA arrays may be useful in the future.[31,32]

The limitations of our study are its restriction to a single medical center, retrospective review method and exclusion of infants who were admitted to the cardiovascular surgery intensive care unit.

5. Conclusions

In conclusion, the majority of infants with early-onset sepsis were term babies. In contrast, late-onset sepsis affected mainly preterm and VLBW babies. Unlike previous reports from Taiwan, GBS was the most common pathogen responsible for early-onset sepsis. GBS screening and IAP guidelines should be popularized in Taiwan to prevent neonatal early-onset sepsis. The leading causative microorganisms in late-onset sepsis were CONS and Candida species. *C. parapsilosis* was associated with a high mortality rate.

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